REMARKS

The Office Action of December 30, 2002 presents the examination of claims 1-18. Claims 1 and 2 are amended. Support for "as a solid particle" is found in the specification, such as on page 12, lines 20-29, wherein the mechanism of infiltration of water into the inside of the drug dispersion is disclosed. Specifically, it is disclosed that water infiltrates into said drug dispersion from a part at which solid particles consisting of a lipophilic drug and a water-soluble substance contact with water. Furthermore, on page 15, lines 1-10 of the specification, several factors which control the release rate of a lipophilic drug from the preparation of the invention are described, including particle sizes of a lipophilic drug, a water-soluble substance and other additives. Thus, the specification clearly supports a lipophilic drug and a water-soluble substance as a solid particle. As such, no new matter is inserted into the application.

Interview

A personal interview was held with the Examiner at the United States Patent and Trademark Office on April 10, 2003. The Examiner's assistance in advancing prosecution of the present application is greatly appreciated.

Rejection under 35 U.S.C. § 103(a)

Paragraphs 2 and 4 of the Office Action

The Examiner rejects claims 1-6 and 8-18 under 35 U.S.C. § 103(a) for allegedly being obvious over Fujioka '547 (U.S. Patent 5,851,547) in view of Fujioka '253 (U.S. Patent 4,985,253). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

In the Reply under 37 C.F.R. § 1.111 filed on October 4, 2002, Applicants pointed out that the drug formulation of Fujioka '547 uses water-soluble drugs (see, e.g., column 4, line 55), whereas the sustained release preparation of the present invention uses a lipophilic drug. In response, on page 5, lines 10-13 of the Office Action, the Examiner alleges that Fujioka '547 discloses both lipophilic and water-soluble drugs, and thusly reads on claims 1 and 10 of the present application. During the interview, the Examiner stated that it is known in the art that some of the drugs listed by Fujioka '547 are lipophilic, such as adriamycin, mitomycins, daunorubicin, and beta-lactams (see column 7, lines 1-6 of Fujioka '547). Even though the Examiner has not made a *prima facie* case of obviousness, since it is not clear on the record that Fujioka '547 discloses lipophilic drugs, Applicants respectfully disagree with the Examiner's assertions that adriamycin, mitomycins, daunorubicin, and beta-lactams are lipophilic drugs for the following reasons.

Adriamycin, mitomycin, and daunorubicin are known in the art as water-soluble drugs as shown in the attached excerpt from MERCK INDEX, TWELFTH EDITION (MERCK & CO., INC. 1996). Adriamycin is described as doxorubicin hydrochloride in the left column on page 582, and is further described as "Sol in water" (i.e., soluble in water). Mitomycins are described in Item 6301 on page 1063 of the Merck Index. The right column on page 1063 describes all of Mitomycin A, Mitomycin B, and Mitomycin C as "Sol in water" (see paragraphs entitled "Mitomycin A," "Mitomycin B," and "Mitomycin C"). Daunorubicin is described in Item 2890 on page 479 of the Merck Index. The right column of page 479 describes the hydrochloride of daunorubicin as "Sol in water." Thus, according to the Merck Index, which is leading publication in the art of pharmaceuticals, adriamycin, mitomycins, and daunorubicin are water-soluble drugs. In contrast, the instant specification describes a lipophilic drug as having a low solubility in water, practically insoluble, very hard to dissolve, or hard to dissolve (see page 11, lines 9-19). The characterization of "Sol in water" from the Merck Index does not correspond to any of these expressions.

"Beta-lactams" are a group of antibiotics that have a beta-lactam nucleus. Both water-soluble and lipophilic antibiotics may be included in the definition of "beta-lactams." However, a person skilled in the art, upon reading Fujioka '547, would understand that the beta-lactams disclosed by Fujioka '547 are

restricted to water-soluble beta-lactams, and do not encompass lipophilic beta-lactams. In column 6, lines 35-36, Fujioka '547 discloses, "Any **water-soluble** drug in this invention may be used that is **not soluble nor diffusible to the outer layer,**…[emphasis added]" and exemplifies peptides, proteins, glycoproteins, polysaccharides, and nucleic acids as such water-soluble drugs (see, column 6, lines 39-40). Fujioka '547 further describes "low-molecular weight drugs such as **water-soluble anticancer agents, antibiotics**…[emphasis added]" as the drugs that can be applied in the drug formulations (see column 6, lines 64-67) and gives specific examples "adriamycin, bleomycins, mitomycins, fluorouracil, peplomycin sulfate, daunorubicin hydrochloride,… **beta-lactams**…[emphasis added]." (See, column 7, lines 1-5). From this description, a person skilled in the art would read "beta-lactams" as an example of the "**water-soluble**…antibiotics", as he/she would for "adriamycin" as an example of "water-soluble anticancer agents." Thus, the beta-lactams disclosed by Fujioka '547 are clearly limited to water-soluble beta-lactams.

For all of the above these reasons, it is clear that Fujioka '547 simply fails to disclose any lipophilic drug. Instead, Fujioka '547 merely teaches the use of a water-soluble drug (see, column 6, line 35 to column 7, line 6 of Fujioka '547). Therefore, the present invention is not obvious to a person skilled in the art from the disclosure of Fujioka '547 and Fujioka '253.

In addition, Fujioka '547 teaches away from the use of lipophilic drugs in his invention. The drug formulation of Fujioka '547 comprises an inner layer containing a water-soluble drug, wherein one or both ends of the inner layer are open to the external environment, and an outer layer composed of a material impermeable to water wherein the outer layer surrounds the circumference of the inner layer. (See, column 3, line 66 to column 4, line 13). With such a construction, the formulation of Fujioka '547 can restrict the water-soluble drug to be released from one or both ends of the inner layer, and thereby, the rate of water infiltration can be subjected to an optimal regulation, and the release of the water-soluble drug can be achieved over prolonged periods of time at a nearly constant rate (zero-order release). Thus, Fujioka '547 exclusively applies the release process of water-soluble drugs to the drug formulation of his invention. On the other hand, a lipophilic drug should be released mainly through the outer layer (cf. page 7 of the Reply under 37 C.F.R. § 1.111 filed on October 4, 2002). Therefore, a person skilled in the art would understand that the desired effect of the Fujioka '547 formulation is not obtainable with a lipophilic drug. For this reason, the drug to be used in the formulation of Fujioka '547 must be "water-soluble" and "not soluble nor diffusible to the outer layer." Consequently, Fujioka '547 teaches away from the use of lipophilic drugs.

On page 5, lines 13-15 of the Office Action, the Examiner points out that Fujioka '547 discloses that the drug formulation may contain two or more drugs. Nevertheless, this matter is irrelevant to the present invention since Fujioka '547 fails to disclose, and teaches away from, a lipophilic drug. Even if the drug formulation of Fujioka '547 can contain two or more drugs, Fujioka '547 merely suggests that the drug formulation may contain two or more water-soluble drugs. Thus, the Examiner's reliance on the disclosure of two or more drugs in Fujioka '547 is misplaced.

The Examiner further states that Fujioka '547 teaches that the drug release from the drug formulation can be adjusted or modulated by a number of techniques such as modifying the type of outer layer material, adjusting the outer layer thickness, varying the drug content of the inner layer and/or size and shape of the drug particles and additive selection (Page 5, lines 15-20 of the Office Action). Again, these features of Fujioka '547 are irrelevant to the present invention. The drug formulation of Fujioka '547 simply does not contain, and even teaches away from, a lipophilic drug. Furthermore, the Examiner fails entirely to provide any motivation permitting one of ordinary skill in the art to use a lipophilic drug in place of, or in addition to, the water-soluble drug(s) in the drug formulation of Fujioka '547. Thus, the reference fails to render the present invention, as recited in the claims, obvious.

In addition, as discussed in the Reply filed on October 4, 2002, the drug formulation of the present invention provides a release of a sufficiently effective amount of a lipophilic drug at a constant rate over a month-order. The drug formulation of the present invention can also release a drug at a significantly greater level than that of the control preparation. As shown in the working example disclosed on page 22 of the specification, the amount of released drug from inventive preparation 1 was about four-fold that of the control preparation (see, Figure 3, 84^{th} day). This effect of the present invention is unexpected and not obvious to the skilled artisan from the disclosures of Fujioka '547 and/or Fujioka '253.

Finally, the use of polyethylene glycol as taught in Fujioka '253 does not influence the non-obviousness of the claimed invention. Fujioka '253 is merely relied upon to teach the use of polyethylene glycol. Fujioka '253 does not make up for the differences between the drug release process for water-soluble drugs and for lipophilic drugs as discussed above.

In summary, the combination of Fujioka '547 and Fujioka '253 fails to render the present invention obvious. Withdrawal of the instant rejection is respectfully requested.

Paragraphs 3 and 4 of the Office Action

The Examiner rejects claims 1-3, 5-7, and 11 under 35 U.S.C. § 103(a) for allegedly being obvious over Kannji '581 (JP 07 330

581). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Claim 1 (as amended) recites, "A sustained release preparation of a lipophilic drug, comprising a drug dispersion wherein the lipophilic drug and a water-soluble substance are dispersed, as a solid particle at the body temperature of an animal or a human being to which the preparation is to be administered, in a water-impermeable and biocompatible material." Thus, a lipophilic drug, a water-soluble substance or a mixture thereof is dispersed as a solid particle in a water-impermeable and biocompatible material. Claim 1 always requires lipophilic drug and a water-soluble substance, while discrete particles can be either or a combination. See figure 1 below.

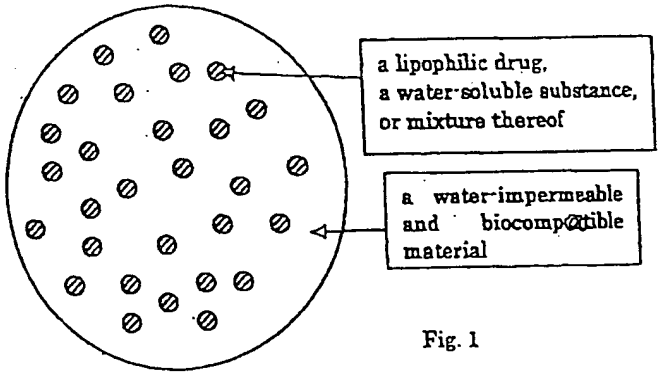

Fig. 1

On the other hand, Kannji '581 discloses a matrix formulation as shown in the following figure 2.

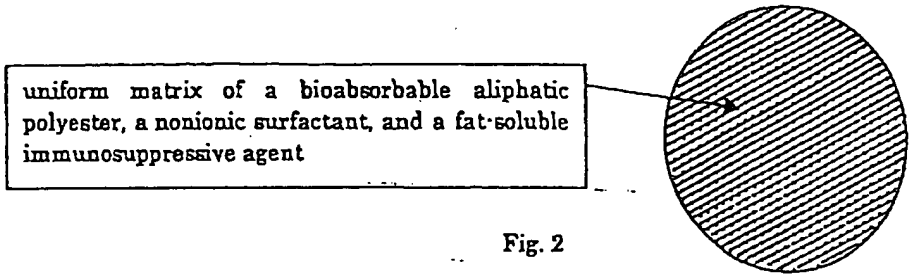

Fig. 2

Applicants respectfully submit that the sustained release immunosuppressive drug disclosed by Kannji '581 fails to meet all of the limitations of claim 1. The sustained release preparation of claim 1 has a construction shown in figure 1, above. The term "as a solid particle" means that a lipophilic drug and a water-soluble substance are dispersed as a solid particle. In contrast, the sustained release immunosuppressive drug disclosed in Kannji '581 has the construction shown in figure 2, above. Although Kannji '581 discloses a drug formulation molded in a solid form, Kannji '581 specifically teaches that in the preparation of such formulation, the agents are completely dissolved in an organic solvent. In such a procedure, the resulting solution is then poured into a die, and the solvents evaporated off to yield a drug formulation. See, page 10, lines 13-19 of Kannji '581. Thus, the drug formulation of Kannji '581, taken as a whole, may be in a solid form, but the lipophilic drug and the water-soluble agent are homogenously dissolved therein,

and therefore are not "as a solid particle." Additionally, a person skilled in the art would not appreciate that the drug formulation of Kannji '581 comprises any particles.

Furthermore, any motivation to comprise such particles in the drug formulation is not found in Kannji '581. Rather, Kannji '581 intends to prevent formation of such particles, and thusly teaches away from a solid particles. For example, Kannji '581 specifically describes the effect of the invention that the immunosuppressive agents are homogeneously dissolved therein and thereby prevents precipitation of the agent. See, page 13, lines 17-18 of Kannji '581. Accordingly, it is apparent that the drug formulation of Kannji '581 cannot have a construction as shown in figure 1, above.

Furthermore, the effect of the claimed invention is unexpected and not obvious to those skilled from the disclosure of Kannji '581. As stated above, the drug formulation of the claimed invention can release a drug over month order at a constant rate, and the rate is significantly greater than that of the control preparation. This effect of the claimed invention is not obvious to those skilled in the art from Kannji '581.

During the interview, the Examiner agreed that "as a solid particle" adequately distinguishes the present invention from Kannji '851, who only discloses a homogeneous drug mixture. The Examiner also agreed that the specification provides adequate support for the amendment. For all of the above reasons, the

invention of claims 1-3, 5-7 and 11 is not obvious to those skilled in the art over Kannji '581. Withdrawal of the instant rejection is respectfully requested.

Summary

Applicants respectfully submit that the above amendments and/or remarks fully address and overcome the rejections of record. The instant claims are now in condition for allowance. Early and favorable action by the Examiner is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. 45,702) at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional

fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: Excerpt from Merck Index, 12th Ed. (Merck & Co., Inc., 1996)
Version with markings showing changes made

VERSION WITH MARKINGS SHOWING CHANGES MADE

In the claims:

Please amend the claims as follows:

1. (Amended) A sustained release preparation of a lipophilic drug, comprising a drug dispersion wherein the lipophilic drug and a water-soluble substance are dispersed, as a solid particle [in a solid state] at the body temperature of an animal or a human being to which the preparation is to be administered, in a water-impermeable and biocompatible material.

2. (Amended) The sustained release preparation of a lipophilic drug as claimed in Claim 1, which is a rod preparation comprising a drug dispersion and a coating layer, wherein

in said drug dispersion the lipophilic drug and the water-soluble substance are dispersed, as a solid particle [in a solid state] at the body temperature of an animal or a human being to which the preparation is to be administered, in a water-impermeable and biocompatible material,

said coating layer comprises a water-impermeable and biocompatible material which is same as or different from that used for said dispersion, and

said drug dispersion is exposed from the surface of the preparation at one or both end(s) of the axial direction thereof.